

# A Primer on Inflammation for Psychiatrists

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## ABSTRACT

The immune system is critical for maintaining homeostasis. It is composed of multiple cell lineages that act in concert to clear pathogens and insults through orchestrated mechanisms comprising immunological recognition, effector functions, immune regulation, and memory. These functions are dependent on the two arms of the immune system: the innate and adaptive immune systems. Some of the complex mechanisms mediated by these systems are described here, including toll-like receptor activation, cytokine production, antigen recognition, and antibody production. Altogether, the immune system's actions are tightly regulated to provide protection against pathogens and insults and to maintain homeostasis. [*Psychiatr Ann.* 2015;45(5):226-231.]

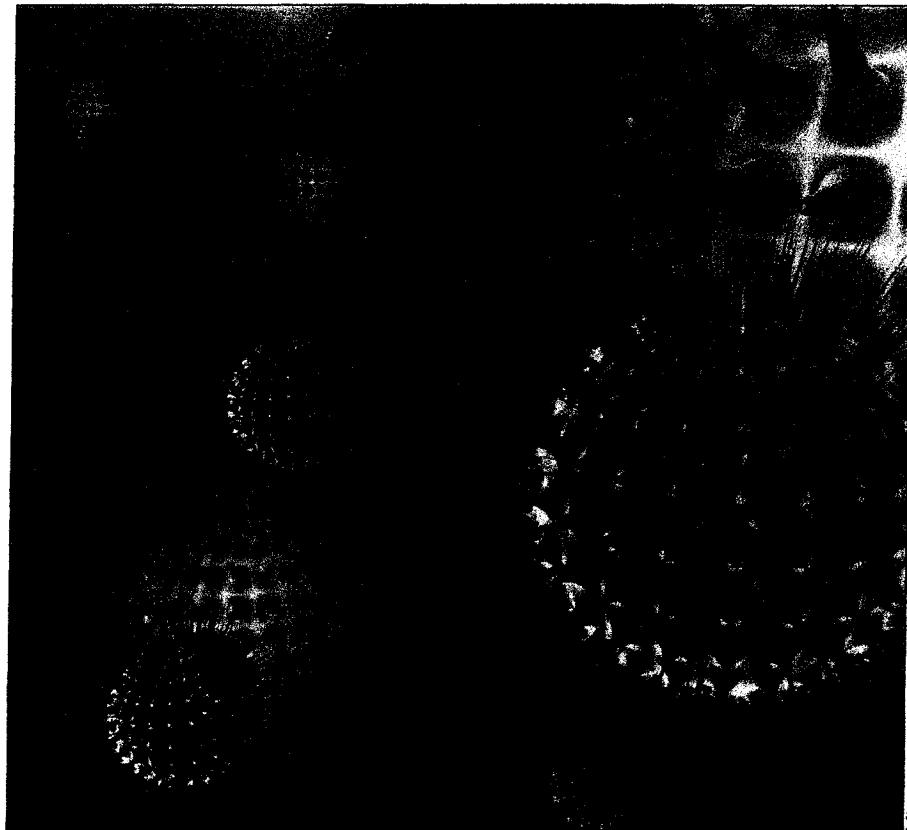
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**T**he body is protected from external insults, such as infectious agents and toxins, and internal insults, such as cancer cells, by the immune system. The immune system comprises a wide variety of cells and molecules that work together to fulfill its four main mechanisms that are directed toward providing protection and maintaining homeostasis in the host.

## MECHANISMS OF ACTION OF THE IMMUNE SYSTEM

The four mechanisms are (1) immunological recognition, (2) immune effector functions, (3) immune regulation, and (4) immunological memory.

### Immunological Recognition

The detection of pathogens and other insults is mediated by a complex and sophisticated network of cells and

receptor signaling pathways that recognize foreign molecules to provide a coordinated immune response.<sup>1</sup>

### **Immune Effector Functions**

The neutralization and clearance of pathogens or insults by the immune system requires the integrated actions of multiple systems, such as the complement system, the systems enabling the production of antibodies, and the effector actions of lymphocytes.<sup>2,3</sup>

### **Immune Regulation**

The toxic mechanisms used by the immune system to eliminate pathogens and insults have the potential to harm the host. Therefore, the immune system must also be a guardian of the host to maintain homeostasis and to avoid damage caused both by external agents and by the immune system's response to them.<sup>4</sup> Failures in these self-regulating mechanisms of the immune system lead to several diseases, such as chronic inflammation, autoimmunity, and allergies.

### **Immunological Memory**

This is also a critical function of the immune system. When the immune system encounters repeated exposures to the same pathogen, its memory systems provide for acceleration of the rate of response and allows it to generate an amplified response to provide protective immunity against the pathogen.<sup>5,6</sup>

### **THE IMMUNE SYSTEM**

The immune system was historically divided into two branches: humoral immunity and cell-mediated immunity (**Figure 1**). Humoral immunity involves molecules present in body fluids (ie, humours) and is mediated by molecules in extracellular fluids, such as antibodies, complement proteins, and antimicrobial peptides. Cell-mediated immunity does not involve antibodies but instead

consists of the release of cytokines in response to an antigen, antigen-specific cytotoxic T cells, and activation of phagocytes. The immune system has more recently been conceived as containing two arms that cooperate with each other—the innate and adaptive immune systems.<sup>7</sup> The innate immune system and the adaptive immune system each comprise both humoral and cell-mediated components. The first of these to be activated is the innate immune system, which provides a quick response to counteract pathogens through the direct production of proinflammatory cytokines after recognition of pathogens.<sup>8</sup> The second of these is the adaptive immune system, which undergoes a slower response that requires antigen-specificity to induce the differentiation and/or clonal expansion of immune cells to mount a full immune response, which usually also includes cytokine production.

All the cells of both arms of the immune system are derived from pluripotent hematopoietic stem cells that reside in the bone marrow (**Figure 2**). These stem cells give rise to progenitors of the lymphoid cells, including T cells, B cells, and natural killer (NK) cells, and progenitors of myeloid cells, including macrophages, granulocytes, mast cells, and dendritic cells, as well as megakaryocytes and red blood cells. These cells also give rise to microglia, which are often considered to be the macrophages of the brain and which carry out macrophage-like functions such as phagocytosis and production of inflammatory cytokines in the central nervous system.

### **MAIN CELLS OF THE LYMPHOID LINEAGE**

Cells from the lymphoid lineage participate in both the adaptive immune system (T and B lymphocytes) and the innate immune system (NK cells). In contrast to cells in the innate immune system, the lymphocytes are antigen-specific. In the absence of infection, most

lymphocytes are small, round cells with little cytoplasm that are constantly present in the circulation but with no known functional activity. These lymphocytes that have never encountered an antigen are considered naïve cells. However, after lymphocytes encounter an antigen they become activated and functional after differentiation into effector cells.

### **T Lymphocytes**

T lymphocytes, also often simply referred to as T cells, express the T-cell receptor (TCR) on the surface of the cell. The TCR is designed to recognize antigens, and when this occurs the T cells become activated, they proliferate, and then differentiate into one of several subsets of effector T cells. Effector T cells have three main functions (activation, regulation, and killing) and are classified as cytotoxic CD8 T cells or helper CD4 T cells. As their name implies, cytotoxic T cells kill cells that are infected by pathogens or viruses. Helper T cells, as their name indicates, help other cells fulfill their actions, such as helping antigen-stimulated B cells to produce antibodies or helping macrophages to more efficiently eliminate engulfed pathogens. Finally, the regulatory subtype of T cells suppresses the activity of other lymphocytes to keep the immune response under control.

There are also subsets of T and B cells that differentiate into memory cells, which are critical for long-lasting immunity. If these memory cells encounter the same antigen again, they can respond quicker than naïve cells by rapidly differentiating into effector cells.

### **B Lymphocytes**

Naïve B lymphocytes, often called B cells, proliferate and differentiate into mature cells in the plasma after activation of the B cell receptor (BCR) by an antigen. Plasma B cells produce antibodies, which are a secreted form of the BCR with an identical antigen specificity

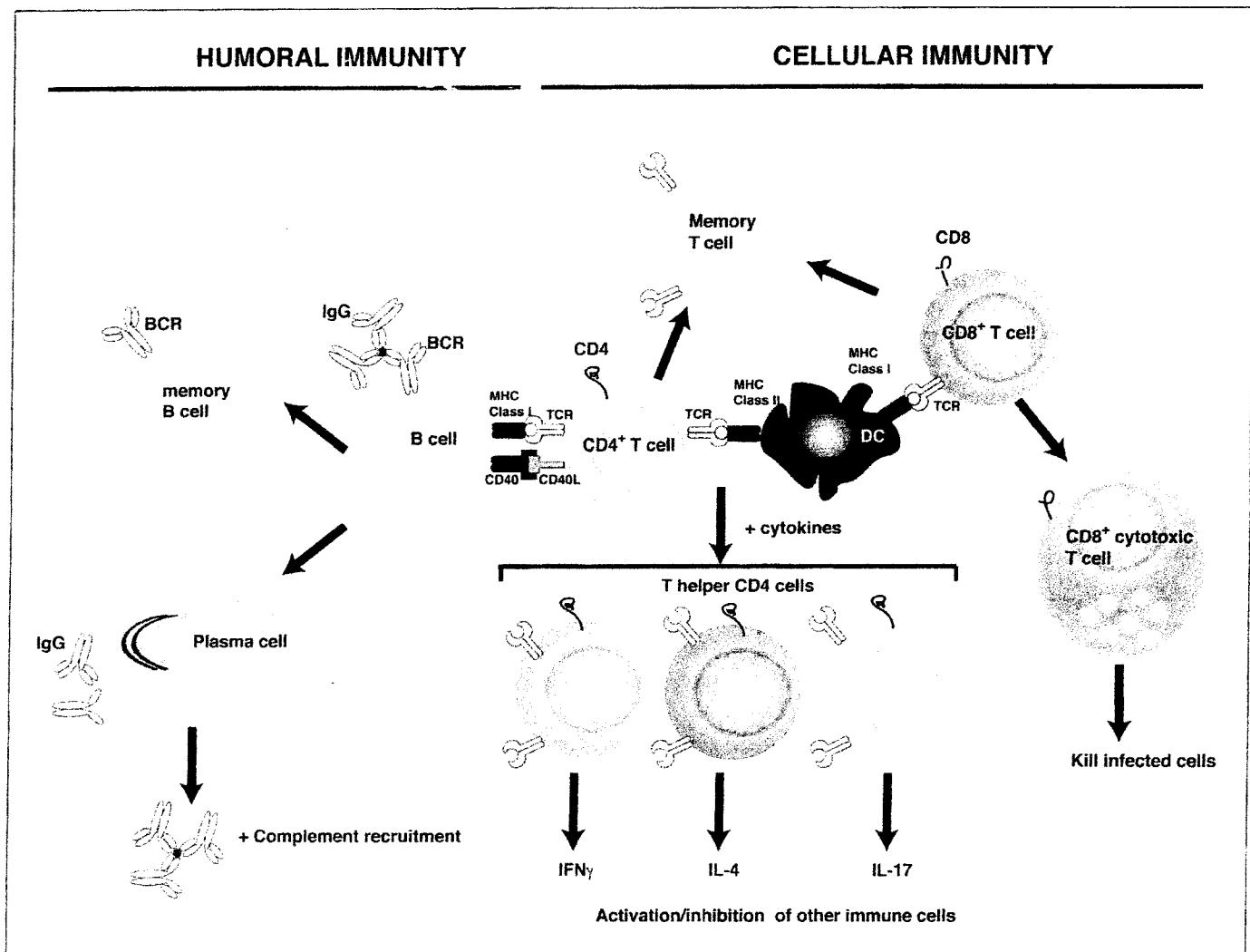


Figure 1. Diagram of humoral and cellular immunity. BCR, B cell receptor; CD, cluster of differentiation; DC, dendritic cell; IFN, interferon; IgG, immunoglobulin G; IL, interleukin; MHC, major histocompatibility complex; TCR, T-cell receptor; Th, T-helper cell.

as the BCR that encountered the pathogenic antigen. This allows the progeny cells to target the antigen with specific antibodies (also called immunoglobulins).

#### Natural Killer Cells

NK cells are not antigen-specific and therefore are not considered members of the adaptive immune system even though they have a lymphoid origin. NK cells are important in the clearance of abnormal cells, such as tumor cells or cells infected by virus, for the latter holding the viral infection in check until the adaptive im-

mune system is activated and ready to participate.

#### MAIN CELLS OF THE MYELOID LINEAGE

##### Macrophages, Monocytes, and Microglia

Macrophages reside in almost all tissues and are derived from monocytes. Monocytes are only found in the blood, and when they migrate to any tissue they become macrophages. Microglia, considered the macrophages of the brain, derive from primitive macrophages that colonize the neuroepithelium early in development after

they exit the yolk sac.<sup>9</sup> Macrophages and monocytes have several functions, including (1) phagocytosis, in which these cells engulf and kill invading microorganisms, which plays a role as a first line of defense and also helps in the elimination of pathogens and infected cells after they are targeted by the slower-acting adaptive immune system;<sup>10</sup> (2) orchestration of the immune response by inducing inflammation, which is the prerequisite for the immune response, and secreting signaling proteins that activate other immune cells and recruit them to the site of the insult or infection;<sup>11</sup> and (3)

scavenging cells, clearing dead cells and cellular debris.<sup>12</sup>

### Neutrophils

The phagocytic neutrophils are the most numerous cells in the innate immune system and are often considered to be the most important cells because they are very efficient in clearing a wide variety of microorganisms by phagocytosis, using degradative enzymes and other antimicrobial molecules that are present in their cytoplasm.<sup>13-15</sup>

### Dendritic Cells

Similar to macrophages and neutrophils, dendritic cells are phagocytic cells and have the particular characteristic of being capable of macropinocytosis, during which they can ingest large amounts of extracellular fluid and its contents. However, their main function is not to clear microorganisms. Once they encounter a pathogen, dendritic cells become mature cells that activate the T lymphocytes, via presentation of the pathogen antigen at the surface, which can be recognized by the TCRs. Therefore, dendritic cells are also called antigen-presenting cells and represent a critical link between the innate and the adaptive immune systems.<sup>16</sup>

Following infection, the first immune response is pathogen recognition by the innate immune system.

## MECHANISMS OF ACTION OF THE INNATE IMMUNE SYSTEM

### TLR Signaling

One of the main signaling pathways that regulates immune responses is initiated by activation of toll-like receptors (TLRs).<sup>17</sup> There are 10 types of TLRs in humans and 13 in mice, and each one is specialized for recognizing specific molecular patterns that are not supposed to be in noninfected vertebrate cells. These molecular patterns are called pathogen-associated molecular patterns (PAMPs).<sup>18,19</sup> Thus, for example, typical

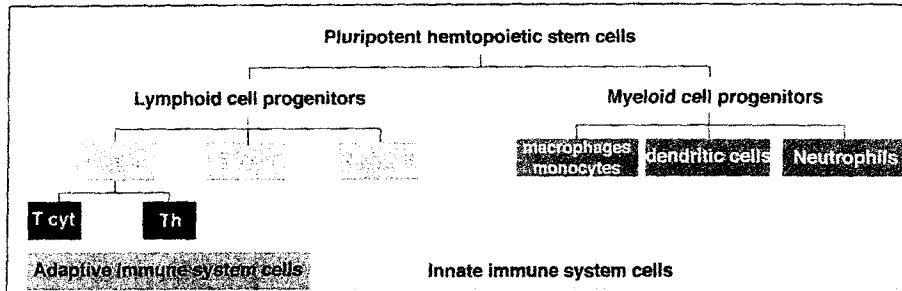


Figure 2. The lineages of major cell types in the immune system and their classification as members of the innate or adaptive immune systems. NK, natural killer; T cyt, T cytokine; Th, T-helper cell.

PAMPs that are recognized by different TLRs, and therefore stimulate signaling by the TLR, include lipoteichoic acids of Gram-positive bacteria, lipopolysaccharide (LPS) of Gram-negative bacteria, bacterial flagella, and bacterial DNA, which has a lot of unmethylated CpG repeats, all having the characteristic of being composed of many repetitive motives. In addition to PAMPs, TLRs can also be activated by endogenous ligands called danger- or damage-associated molecular patterns (DAMPs).<sup>20</sup> As their name indicates, DAMPs are molecules that are produced or released by cells following many types of stress, such as oxidative stress, as opposed to the infection-induced PAMPs, and increased levels of DAMPs have been detected in the central nervous system after many conditions that cause neuronal damage. Although ligand-selectivity provides a degree of specificity, TLRs contain limited specificity compared to the antigen receptors of the adaptive system, but TLRs have the advantage of being widely expressed.

Among the most noted TLRs is TLR4, which recognizes bacterial lipopolysaccharides and is responsible for the induction of sepsis.<sup>21,22</sup> In the presence of the signaling proteins CD14 and MD-2, activation of a TLR leads to a diverse range of intracellular responses, resulting in the production of inflammatory cytokines, chemokines, antimicrobial peptides, and the antiviral cytokines interferon (IFN)-alpha and IFN-beta. Signaling pathways that have been identified in mediating

the intracellular response to stimulation of TLRs include activation of the transcription factor nuclear factor-kappa B (NF- $\kappa$ B) and of several members of the interferon regulatory factor (IRF) family, which are the most common pathways used by TLRs. Other transcription factors, such as AP-1 (activator protein 1), and intracellular signaling mediators, such as mitogen-activated protein kinases, have also been shown to be important in TLR response.<sup>23,24</sup>

In the process of activation, TLRs form dimers. This dimerization causes a change in the conformation of the TLRs that initiates the recruitment of intracellular adaptor proteins, including MyD88 (myeloid differentiation factor 88), TRIF (TIR domain-containing adaptor-inducing IFN-beta), MAL (MyD88 adaptor-like), and TRAM (TRIF-related adaptor molecule). Different combinations of these adaptors are activated after stimulation of different TLR receptors. MyD88 interacts with two serine-threonine kinases, IRAK4 (IL-1-receptor associated kinase 4) and IRAK1, which in turn bind to the E3 ubiquitin ligase TRAF6 (TNF receptor-associated factor 6). This leads to the activation of TAK1 (transforming growth factor beta-activated kinase 1), another serine-threonine kinase. TAK1, by phosphorylating the IkappaB kinase complex (IKK), activates IKK, which in phosphorylates IkappaB, leading to the release of active NF- $\kappa$ B that can then migrate to the nucleus and activate the transcription of cytokines.

## Cytokines

Cytokines are small molecules that are secreted by a variety of cells from both the innate and the adaptive immune systems, and cytokines can act in an autocrine, paracrine, or endocrine manner.<sup>1</sup> Some of the common cytokines secreted by activated dendritic cells and macrophages are interleukin-1 beta (IL-1beta), IL-6, IL-12, tumor necrosis factor-alpha (TNF-alpha), and IL-8 (also called CXCL8). Cytokines have been classified into four main families: (1) the IL-1 family comprised of IL-1 and IL-18, which need to be cleaved to become activated; (2) the TNF family, which includes TNF-alpha and 17 other cytokines, such as lymphotoxin-beta; (3) the type I IFN family, including IFN-alpha, INF-beta, and several other interferons; and (4) the hematopoietins, including IL-6, macrophage colony-stimulating factor, granulocyte macrophage colony-stimulating factor, and also erythropoietin, which promotes the growth of nonimmune system cells. The IL-1 family activates NF-kB similarly to the TLRs. The hematopoietins signal through either INF receptors or hematopoietin receptors, which activate the JAK-STAT (janus kinase–signal transducer and activator of transcription) pathway. TNF-alpha is bound to the membrane in a trimeric structure and is released from the membrane following stimulation to activate tumor necrosis factor receptor (TNFR)-I and TNFR-II. TNFR-I is expressed in a wide range of cells, including macrophages, whereas TNFR-II is only expressed on lymphocytes.<sup>25</sup>

Due to the high number of cytokines, it is thought that during their evolution each emerged with very specialized functions dependent on the upstream signaling pathway leading to cytokine production, the pathogen encountered, and the cells that secrete the cytokines. All of this converges to mount a proper immune response that is critical for transition to the next phase of the host de-

fense and causes many of the symptoms of sickness.<sup>26</sup> These symptoms include the increase of the body's temperature, mainly due to IL-1beta, TNF-alpha, and IL-6 through the synthesis of prostaglandin E2 and cyclooxygenase-2, which act on the hypothalamus to increase body temperature.<sup>27</sup> The same cytokines are also important for the initiation of the

*Cytokines are small molecules that are secreted by a variety of cells.*

acute-phase response by acting on hepatocytes to induce the production of the acute-phase proteins. These proteins seem to play the role of antibodies without having antibody specificity. Thus, for example, C-reactive protein is a common acute-phase protein that can bind to the bacterium directly, opsonize it, and also activate the complement system.<sup>28</sup> Finally, cytokines can also promote leukocytosis, the increase in the number of circulating neutrophils that leads to improved control of the infection during the time that the adaptive immune system is being recruited.

## Activation of the Adaptive Immune System

To effectively fight pathogens, the immune system needs to be able to recognize a remarkably broad range of pathogens.<sup>29</sup> This can be achieved by the adaptive immune system through the creation of libraries of receptors on lymphocytes that can recognize a variety of antigens. Each B cell produces an antigen-specific immunoglobulin. The immunoglobulins have two main functions: (1) binding to the pathogen (recognition function) and (2) recruiting other cells or molecules to destroy it (effector function).<sup>30</sup> The recognition is mediated by the variable region of the immuno-

globulin, whereas the effector function requires the constant region. B cells also express a B-cell receptor (BCR) that is equivalent to an immunoglobulin except that they do not have an effector function because the constant region is inserted in the membrane. However, a BCR recognizes the pathogen through the variable region and promotes the clonal expansion of B cells and the production of antibodies.

Similarly, T cells express a TCR that is bound to the membrane and activates T cells. A TCR alone is not sufficient to recognize the pathogen, but instead it requires the presentation of antigen peptide fragments by the proteins of the major histocompatibility complex (MHC). There are two classes of MHC: MHC class I and MHC class II. MHC class I proteins transport cytosolic peptides incorporated at the endoplasmic reticulum, and MHC class I-derived peptides are recognized by CD8 T cells. MHC class II proteins, in contrast, incorporate peptides degraded in endosomal vesicles, and MHC class II-derived peptides are recognized by CD4 T cells. CD4 and CD8 T cells have different antipathogen activities; therefore, the MHC class is important in directing the CD4/CD8 response.<sup>31</sup>

Naïve CD4 or CD8 T cells that encounter a cell-presenting antigen with the appropriate peptide/MHC ligand will initiate the T-cell responses. The first signal is adhesion with the antigen-presenting cells, which leads to clonal expansion and the differentiation of naïve T cells. To induce complete activation of the T cells, at least three signals should be encountered, comprising the recognition of the peptide/MHC, a co-stimulatory signal (eg, CD28), and a signal that directs the T-cell differentiation into the different subsets of effector T cells.<sup>32</sup> Without co-stimulation, T cells are discarded. CD8 T cells all differentiate into cytotoxic T cells, whereas CD4 T cells can differentiate into several subsets, com-

prising T helper (Th)1, Th2, Th17, and regulatory T cells. For differentiation to each subset of T cells, Th1 cells require IL-12, Th2 cells require IL-4, Th17 cells require IL-6 and TGF-beta, and regulatory T cells require TGF-beta.<sup>33</sup>

There are two broad classes of effector functions of T cells: (1) the cytotoxins, which are released by the cytotoxic CD8 T cells and that are specialized cytotoxic granules comprising perforin and granzymes and have no specificity for the targeted cells because they can penetrate any lipid membrane to trigger apoptosis,<sup>34</sup> and (2) the cytokines and membrane proteins that are *de novo* synthesized by all effector cells. In the case of CD4 T cells, actions of the cytokines and the membrane proteins are restricted to cells with the MHC class II molecules and the receptors for these molecules.

## CONCLUSION

The immune system comprises many cell types that have developed a diverse array of specific mechanisms to clear pathogens or to recover from insults while also striving to maintain homeostasis in the host. Any dysregulation of this system can have detrimental consequences to the host, such as causing autoimmune diseases.

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